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Association between alcohol consumption and diabetic retinopathy and visual acuity—the AdRem Study

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Abstract

Aims We investigated the association between alcohol consumption and diabetic retinopathy and deterioration of visual acuity in individuals with Type 2 diabetes.

Methods We conducted a cohort analysis of 1239 participants with Type 2 diabetes aged 55–81 years enrolled in the AdRem study, a sub-study of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial. Current and past consumption of wine, spirits and beer was measured by self-report. Moderate and heavy alcohol consumption was defined as 1–14 and > 14 drinks/week, respectively. Diabetic retinopathy, measured by mydriatic stereoscopic seven-field retinal photography, was defined by a 2-step progression in the Early Treatment of Diabetic Retinopathy Study (ETDRS) score or the presence of any retinal vascular lesions. Deterioration of visual acuity was defined by a decrease of two lines in best vision in either eye, measured corrected, or through a pinhole using a Snellen chart.

Results In a mean follow-up of 5.5 years, we identified 182 participants with a 2-step progression in the ETDRS score, 640 participants with the presence of any retinal vascular lesions and 693 participants with a deterioration of visual acuity. Current moderate consumption of alcohol, compared with no current consumption, was not associated with presence or progression of diabetic retinopathy; however, it was associated with higher risk of deterioration of visual acuity (multivariable-adjusted OR 1.83; 95% CI 1.34–2.48; $P < 0.001$).

Conclusions Alcohol consumption is associated with increased risk of deterioration of visual acuity, but not with retinopathy in individuals with Type 2 diabetes.

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Keywords alcohol consumption, diabetic retinopathy, visual acuity

Abbreviations ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation Trial; AdRem, ADVANCE Retinal Measurement Study; ETDRS, Early Treatment of Diabetic Retinopathy Study; logMAR, logarithm of the minimum angle of resolution

Introduction

Retinopathy is a serious microvascular complication of diabetes mellitus. Diabetic maculopathy can cause loss of vision. Lifestyle factors, including alcohol consumption, may alter the risk of retinopathy or visual loss in individuals with diabetes. One of the proposed pathological mechanisms for diabetic retinopathy is inflammation [1]. Moderate alcohol consumption, as compared with no or occasional consumption, has been associated with lower concentrations of C-reactive protein and improved glycaemia through increased insulin sensitivity [2,3]. However, alcohol is toxic to neurological tissues, including the retina, and heavy consumption may induce oxidative stress in these tissues and impair vision [4].

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Limited epidemiological evidence for the association between alcohol consumption and diabetic eye disease exists. Previous studies on alcohol consumption and diabetic retinopathy showed differing results [5–9]. However, these studies were limited by either cross-sectional designs or small sample sizes. No prior study has examined the association between alcohol consumption and deterioration of visual acuity in individuals with diabetes.

In this study, we explore the hypothesis that alcohol consumption is associated with the incidence and progression of diabetic retinopathy and the deterioration of visual acuity among individuals with Type 2 diabetes in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Retinal Measurement (AdRem) study. The main results of the AdRem study have been reported [10].

Research designs and methods

Study population

The study population consisted of participants included in the AdRem study. AdRem, a sub-study of the ADVANCE trial, is a randomized controlled trial of blood pressure lowering and intensive glucose control among individuals with Type 2 diabetes from 39 centres in 14 countries from Asia, Australia, Europe and North America with access to retinal cameras. Ethics approval was obtained from the institutional review board of each centre. All participants provided written informed consent [10].

Participants eligible for the ADVANCE trial were diagnosed with Type 2 diabetes at age 30 or older, were aged 55 or older at entry and were at high risk of vascular disease, as defined by either a diagnosis of diabetes of 10 years or more at entry, or age 65 or older at entry, or a history of cardiovascular disease or other complications of diabetes, or having at least one of a number of other risk factors for vascular disease [11]. Exclusion criteria for the AdRem study included previous ophthalmological interventions in either one or both eyes, which might interfere with retinal circulation, or the presence of severe cataracts or pupils unable to dilate to 4 mm, which prevented quality stereoscopic photographs [11]. Details of the study population have been described [11,12].

Measurement of anthropometry, blood pressure and biochemical variables were performed. Information on ethnicity, duration of diabetes, exercise, cigarette smoking, medications and family history of diabetes were collected in the baseline questionnaire. Ethnicity was classified as Caucasian/European, Chinese, South Asian/South-East Asian and 'others', which included mainly individuals of Arab, African or mixed ethnicity [11].

Measurement of alcohol consumption

Current and past alcohol consumption was measured by self report in the baseline questionnaire. Participants reported the number of standard drinks of wine, beer or spirits consumed per week on average currently and in the past, prior to their diagnosis of diabetes. For example, if the standard size of spirit was 1.5 oz (45 ml) and if a participant consumed a 6-oz (180 ml) glass, he would have reported four standard drinks. The question on alcohol intake was phrased to report the standardized size of consumption for each country. In this study, we assumed that a standard drink had the same size across study centres. Alcohol consumption was categorized into moderate intake (1–14 drinks/week) and heavy intake (>14 drinks/week) using 0 drinks per week as the reference category. In a sensitivity analysis, we re-categorized alcohol consumption into low intake (1–7 drinks/week), moderate intake (8–14 drinks/week) and heavy (>14 drinks/week). Participants were also asked whether they had decreased alcohol intake because of their health. In additional to ethnicity, we adjusted for study centre to account for the variation of serving size and strength of alcohol between countries.

Retinal photography and testing for visual acuity

Stereoscopic photographs were taken with 35-mm high-quality colour film (Kodak EPR64 135-36) of both eyes according to the seven-field Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol at baseline, biennial follow-up and final visits. The seven fields include one centred on the optic disc, one centred on the macula, one temporal to the macula, two superior and two inferior fields. In the AdRem study, diabetic lesions were graded in each field by comparing them with the ETDRS standard photographs according to the modified ETDRS classification [13]. The diabetic lesions were used to define the endpoint of 2-step progression on the ETDRS scale. Vascular lesions were graded in each field according to the Atherosclerosis Risk in Communities Study protocol [14]. Retinal photographs were graded centrally in the AdRem Sub-study Coordination Centre at the University Medical Centre Utrecht, the Netherlands.

Trained researchers tested visual acuity as a part of clinical assessment at baseline and at the final visits following a standardized protocol. Best corrected visual acuity was measured in both eyes (corrected by glasses or contact lens, or through a pinhole) using a Snellen chart at a distance of 6 metres. Participants covered the eye not being tested. The best score for visual acuity was recorded for each eye using metric notation from the Snellen chart, where the numerator was '6 metres' [15]. The denominators were based on the Snellen metric notation. Table 1 shows the conversion of the Snellen metric notation to imperial and decimal notations. Visual impairment at baseline was defined as a best-corrected visual acuity of less than 6/6 in the Snellen metric notation or equivalent.

Definition of outcomes

Outcomes of diabetic retinopathy were defined as either a 2-step progression of diabetic lesions in the modified ETDRS score based on the worst eye or the presence of any retinal vascular

Table 1 Conversion for the measurement of visual acuity in the AdRem Study

Snellen notation (metric)	Snellen notation (imperial)	Decimal
6/6000†	20/20000	0.001
6/600*	20/2000	0.01
6/120‡	20/400	0.05
6/90	20/300	0.07
6/75	20/250	0.08
6/60	20/200	0.10
6/52.5	20/175	0.11
6/50	20/160	0.12
6/45	20/150	0.13
6/37.5	20/125	0.16
6/36	20/120	0.17
6/30	20/100	0.20
6/24	20/80	0.25
6/21	20/70	0.29
6/18	20/60	0.33
6/15	20/50	0.40
6/12	20/40	0.50
6/9	20/30	0.67
6/8.5	20/28	0.71
6/7.5	20/25	0.80
6/6.7	20/22	0.90
6/6	20/20	1.00
6/5	20/16	1.20
6/4.5	20/15	1.33
6/4	20/13	1.50
6/3	20/10	2.00

*Count fingers at 2 feet (0.6 metres).
†Hand motion at 2 feet (0.6 metres).
‡World Health Organization's definition of blindness.

lesions at the final visits, including arteriovenous nicking, microaneurysms, retinal haemorrhages, cotton-wool spots, hard exudates and macular oedema These retinal vascular lesions were either presented at baseline or developed between baseline and final visits. Deterioration of visual acuity was defined as a decrease of two lines or more from the Snellen metric notation (or equivalent in imperial or decimal notations; Table 1) in best vision in either or both eyes between the baseline and the final visits.

Statistical analyses

Characteristics at baseline, including means and standard deviations for continuous variables and percentages for categorical variables, were described. We used analysis of variance and χ^2-tests to test whether continuous and categorical variables differed across level of alcohol consumption. We used multivariable logistic regression analyses to explore the association between current and past alcohol consumption and outcomes of diabetic retinopathy and deterioration in visual acuity. Odds ratios, using 0 drinks/week as the reference category, were used to estimate relative risk and were presented with 95% confidence intervals. In the base model, we adjusted for interventions for treatment of blood glucose and blood pressure. We included covariates in multivariable models if they were of *a priori* clinical relevance or if inclusion substantially influenced the observed odds ratios. Potential confounders included age, sex, cigarette smoking, BMI, HbA_{1c}, systolic blood pressure, duration of diabetes and ethnicity. We reported the *P*-value for a linear trend across level of alcohol consumption.

In a sensitivity analysis, we also modelled alcohol consumption as a continuous variable. We stratified the analyses by ethnic groups (Caucasians vs. non-Caucasians) and tested whether the associations between alcohol consumption and diabetic retinopathy or deterioration of visual acuity differed by ethnic groups using the χ^2-test. We repeated the multivariable analyses after excluding participants who were heavy drinkers in the past but currently abstained from alcohol. For analysis specific for a given type of alcoholic beverage, for example, beer or wine, we also adjusted for consumption of other types of beverage in the fully adjusted models. To assess whether the association of alcohol differed with cigarette smoking, we included an interaction term between smoker vs. non-smokers and level of alcohol consumption. To assess if the presence of cataract, macular oedema or visual impairment at baseline account for the association between alcohol consumption and deterioration of visual acuity, we additionally adjusted for these covariates in the multivariable-adjusted analyses. Statistical analyses were performed using STATA 9.0 (Stata Corporation, College Station, TX, USA).

Results

After excluding two participants with missing data on consumption of alcohol at baseline, these analyses included 1239 participants with retinal photographs from baseline and final visits and with data on deterioration of visual acuity. Characteristics at baseline of the study population by level of current alcohol consumption are shown in Table 2. The average age of participants was 65 years. Alcohol drinkers had higher values for BMI, waist–hip ratio and systolic blood pressure, but a lower level of HbA_{1c} than those who drank no alcohol. Participants who consumed alcohol were more likely to smoke and to be physically inactive. Moderate drinkers had lower prevalence of retinopathy and visual impairment and shorter duration of diabetes at baseline, as compared with non-drinkers or heavy drinkers. Substantial ethnic differences existed in the pattern of alcohol consumption. A higher proportion of Caucasians acknowledged drinking alcohol than Chinese or South Asians. The characteristics at baseline did not differ between participants who consumed alcohol in the past and those consumed currently (data not shown).

After a mean follow-up of 5.5 years, of 1239 participants we identified 182 participants with a 2-step progression in the ETDRS score, 640 participants with the presence of any retinal vascular lesions and 693 participants with a deterioration of visual acuity. We observed no associations between current alcohol consumption and the 2-step progression of ETDRS score

Table 2 Baseline characteristics by levels of current alcohol consumption (n = 1239)

	Current alcohol consumption		
Drinks/week	0	1–14	>14
Number (%)	833 (67.2)	316 (25.5)	90 (7.3)
Alcohol consumption (drinks/week)			
Wine	0	1.7 ± 2.8	4.6 ± 8.1*
Spirits	0	1.3 ± 2.7	9.8 ± 13.3*
Beer	0	2.5 ± 3.1	13.3 ± 16.7*
Age (years)	65.0 ± 5.5	65.1 ± 6.0	65.5 ± 5.01
Sex—male (%)	49.7	79.8	95.6*
Ethnicity (%)			
Caucasian	30.3	73.7	76.7*
Chinese	54.9	14.9	20.0
South Asian	12.7	7.3	2.2
Others	2.2	4.1	1.1
Duration of diabetes (years)	7.5 ± 6.2	6.4 ± 5.4	7.1 ± 6.3*
Current smoker (%)	13.0	17.1	22.2*
Exercise (%)	33.6	24.7	25.6*
Parental history of diabetes (%)			
1 parent	23.7	29.4	27.8
2 parents	2.8	1.9	4.4
Baseline retinopathy (%)	41.8	29.8	37.8*
Baseline visual impairment (%)	66.2	51.3	58.9*
BMI (kg/m^2)	27.3 ± 4.8	28.4 ± 4.4	28.7 ± 5.3*
Waist–hip ratio	0.92 ± 0.07	0.95 ± 0.07	0.98 ± 0.06*
HbA_{1c} (%)	7.2 ± 1.3	6.8 ± 1.0	6.8 ± 1.2*
Glucose (mmol/l)	8.5 ± 3.0	8.3 ± 2.1	8.6 ± 2.6
Triglyceride (mmol/l)	2.0 ± 1.3	1.9 ± 1.1	1.9 ± 1.1
LDL cholesterol (mmol/l)	3.1 ± 0.9	3.1 ± 0.9	2.9 ± 0.8
Total cholesterol (mmol/l)	5.2 ± 1.1	5.2 ± 1.1	5.0 ± 1.0
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.4
Systolic blood pressure (mmHg)	134 ± 20.1	137 ± 21.5	138 ± 19.2*
Diastolic blood pressure (mmHg)	76.0 ± 10.2	79.4 ± 10.6	78.8 ± 10.0*
Insulin use (%)	0.96	0.95	0
Blood pressure medication use (%)	71.5	66.5	68.9
Oral hypoglycaemic agent use (%)	91.4	79.8	90.0*
Participants allocated into treatment for blood pressure (%)	50.5	49.1	48.9
Participants allocated into treatment for intensive glucose control (%)	52.1	48.7	44.4

Data are mean ± standard deviation, unless otherwise indicated.
*P < 0.05.

in either unadjusted or multivariable-adjusted logistic regression models. Logistic regression analysis adjusted for age and sex showed a protective association (P for trend = 0.02) of current consumption of alcohol on the presence of any retinal vascular lesions at follow-up, comparing 1–14 drinks/week (odds ratio 0.65, 95% confidence interval 0.49–0.85) with no consumption. After adjusting for potential confounders, the association was no longer statistically significant. Ethnicity confounded and strengthened the association between alcohol and diabetic retinopathy or deterioration of visual acuity (Table 3).

For visual acuity, we observed an association between current alcohol consumption and the deterioration of visual acuity at follow-up in the age- and sex-adjusted regression model, comparing moderate and heavy consumption with no consumption (P for trend < 0.001). After adjusting for potential confounders, the association strengthened to an odds ratio of 1.83 (95% confidence interval 1.34–2.48) for 1–14 drinks/week and of 2.09 (95% confidence interval 1.28–3.40) for >14 drinks/week (Table 3). Similar significant results for the same comparisons were observed for past alcohol consumption (odds ratio 1.60, 95% confidence interval 1.17–2.19 for 1–14 drinks/week and odds ratio 2.16, 95% confidence interval 1.46–3.20 for >14 drinks/week; P < 0.001). When modelling alcohol consumption as a continuous variable, we observed a 2% increase in the risk of deterioration of visual acuity for each additional alcoholic drink consumed per week (multivariable-adjusted odds ratio 1.02; 95% confidence interval 1.00–1.04, P = 0.01).

As ethnicity confounded the association between alcohol and diabetic retinopathy and deterioration of visual acuity, we stratified the multivariable regression analyses by ethnic groups (Caucasians vs. non-Caucasians). For progression of retinopathy

Table 3 Estimated odds ratios (95% confidence intervals) on the association between alcohol consumption and diabetic retinopathy and deterioration of visual acuity

	Current alcohol consumption			
Drinks/week	0	1–14	>14	*P*-value*
2-steps change in ETDRS score				
Cases	133/833	42/316	12/90	
Model 1	1.0	0.81 (0.55, 1.19)	0.82 (0.42, 1.57)	0.3
Model 2	1.0	0.94 (0.63, 1.41)	0.92 (0.47, 1.80)	0.7
Model 3	1.0	1.08 (0.70, 1.67)	1.07 (0.54, 2.13)	0.8
Any retinal vascular lesion				
Cases	456/833	139/316	45/90	
Model 1	1.0	0.65 (0.49, 0.85)	0.83 (0.53, 1.30)	0.02
Model 2	1.0	0.73 (0.55, 0.97)	0.91 (0.57, 1.46)	0.1
Model 3	1.0	0.88 (0.65, 1.20)	1.08 (0.66, 1.75)	0.9
Deterioration of visual acuity				
Cases	435/833	200/316	58/90	
Model 1	1.0	1.70 (1.29, 2.25)	1.86 (1.16, 2.96)	<0.001
Model 2	1.0	1.76 (1.33, 2.34)	1.93 (1.20, 3.10)	<0.001
Model 3	1.0	1.83 (1.34, 2.48)	2.09 (1.28, 3.40)	<0.001

The base model is adjusted for treatment interventions for blood glucose and blood pressure.
Model 1: age, sex-adjusted.
Model 2: model 1 + HbA_{1c}, systolic blood pressure, duration of diabetes, BMI, cigarette smoking.
Model 3: model 2 + ethnicity.
**P*-value is for a linear trend across levels of alcohol consumption.
ETDRS, Early Treatment of Diabetic Retinopathy Study.

Table 4 Estimated odds ratios (95% confidence intervals) on the association between alcohol consumption and diabetic retinopathy and deterioration of visual acuity, stratified by ethnicity

	1–14 drinks/week		
	Caucasian	Non-Caucasian	$P_{\text{ethnic dierence}}$
2-steps change in ETDRS score	0.84 (0.46, 1.55)	1.50 (0.82, 2.76)	0.2
Any retinal vascular lesions	0.91 (0.62, 1.35)	0.75 (0.45, 1.25)	0.6
Deterioration of visual acuity	1.63 (1.10, 2.41)	2.61 (1.54, 4.44)	0.2
	>14 drinks/week		
	Caucasian	Non-Caucasian	$P_{\text{ethnic dierence}}$
2 steps change in ETDRS score	1.06 (0.43, 2.57)	1.27 (0.40, 4.08)	0.8
Any retinal vascular lesions	0.99 (0.55, 1.76)	1.73 (0.45, 4.60)	0.4
Deterioration of visual acuity	2.11 (1.17, 3.82)	1.71 (0.68, 4.29)	0.7

Multivariable regression models adjusted for blood pressure treatment intervention, blood glucose treatment intervention, age, sex, HbA_{1c}, systolic blood pressure, duration of diabetes, BMI and cigarette smoking.
ETDRS, Early Treatment of Diabetic Retinopathy Study.

and deterioration of visual acuity, the odds ratios for moderate drinking (1–14 drinks/week) were lower among Caucasians than non-Caucasians, but these differences were not statistically significant (Table 4).

For analyses of specific alcoholic beverages, current moderate consumption of each of wine, beer or spirits were all associated with deterioration of visual acuity at follow-up, as compared with no current consumption of each type of the alcoholic beverages. The magnitude of association was stronger with an increased amount of consumption of beer or spirits, in comparison with wine (Table 5). None of the specific alcoholic beverages were associated with the progression of retinopathy or presence of retinal vascular lesions. We observed similar results when we repeated the beverage-specific analyses using past consumption of each type of alcoholic beverages as exposures (data not shown).

In sensitivity analyses, when including study centre, diastolic blood pressure, exercise, retinopathy and visual impairment at baseline, the presence of cataract or macular oedema in the regression models, we observed minimal change in the

Table 5 Estimated odds ratios (95% confidence intervals) on the association between types of alcoholic beverages and diabetic retinopathy and deterioration of visual acuity

	Current alcohol consumption			
Drinks/week	0	1–14	>14	*P*-value*
Wine consumption				
2 steps change in ETDRS score	1.0	1.00 (0.58, 1.72)	—	0.6
Any retinal vascular lesion	1.0	0.80 (0.55, 1.15)	0.61 (0.16, 2.30)	0.1
Deterioration of visual acuity	1.0	1.63 (1.12, 2.37)	0.94 (0.25, 3.47)	0.03
Beer consumption				
2 steps change in ETDRS score	1.0	0.96 (0.56, 1.64)	0.97 (0.36, 2.67)	0.9
Any retinal vascular lesion	1.0	0.83 (0.58, 1.19)	1.38 (0.69, 2.77)	1.0
Deterioration of visual acuity	1.0	1.62 (1.12, 2.33)	2.47 (1.17, 5.18)	0.01
Spirits consumption				
2 steps change in ETDRS score	1.0	0.95 (0.53, 1.73)	2.14 (0.85, 5.36)	0.3
Any retinal vascular lesion	1.0	1.08 (0.72, 1.62)	1.26 (0.56, 2.81)	0.5
Deterioration of visual acuity	1.0	1.44 (0.95, 2.18)	1.95 (0.86, 4.45)	0.03

Multivariable regression models adjusted for blood pressure treatment intervention, blood glucose treatment intervention, age, sex, HbA_{1c}, systolic blood pressure, duration of diabetes, BMI, cigarette smoking, ethnicity and other types of alcoholic beverage.
**P*-value is for a linear trend across levels of alcohol consumption.
ETDRS, Early Treatment of Diabetic Retinopathy Study.

magnitude of the associations between alcohol and diabetic retinopathy or deterioration of visual acuity. Excluding the participants who drank heavily in the past and had given up alcohol for reasons of ill health did not change our results materially. We observed similar results when we re-categorized alcohol consumption into none (0 drinks/week), low (1–7 drinks/week), moderate (8–14 drinks/week) and heavy (>14 drinks/week). In addition, we did not find an interaction between alcohol consumption and cigarette smoking ($P = 0.4$).

Discussion

In this multi-centre study of individuals with Type 2 diabetes, alcohol consumption was not associated with retinopathy as defined by a 2-step progression in the ETDRS score or the presence of any retinal vascular lesions at follow-up. However, those who consumed alcohol were more likely to have experienced a decline in their visual acuity at follow-up when compared with those who abstained from alcohol. The magnitude of this association increased with increasing amounts of alcohol consumed and was unchanged after adjusting for potential confounders.

Our results for retinopathy are consistent with a previous cohort study of patients with either Type 1 or Type 2 diabetes [5]. In the Casteldaccia Eye Study, daily consumption of alcohol for 20 years or more, as compared with no consumption, was inversely associated with diabetic retinopathy in unadjusted, but not in multivariate-adjusted, analyses [7]. Similarly, in the Beijing Eye study, diabetic participants who consumed alcohol of any amount, as compared with those who did not consume alcohol, was associated with a lower risk of retinopathy in unadjusted analysis, but the association attenuated after adjusting for potential confounders [9]. By contrast, the EURODIAB Prospective Complications Study of Type 1 diabetes showed a reduced risk of retinopathy with moderate alcohol consumption in multivariable-adjusted analyses [6]. Although we did not observe an overall protective association of moderate alcohol consumption on diabetic retinopathy, we observed in Caucasians a non-significant inverse association between moderate alcohol consumption and progression of retinopathy and presence of retinal vascular lesions.

This study showed that both moderate and heavy alcohol consumption were associated with a decline in visual acuity in a population with Type 2 diabetes. The relationship with the decline in visual acuity was continuous through the distribution of alcohol consumption. An additional alcoholic drink consumed per week was associated with a 2% increase in risk of decline in visual acuity. To our knowledge, no previous study has shown this association. In a meta-analysis of observational studies, heavy consumption of alcohol, defined as more than three standard drinks per day, was associated with an increased risk of early age-related macular degeneration in the general population [16], the leading cause of blindness in developed countries [17,18]. Large population-based prospective studies on the association between alcohol consumption and the risk of cataract showed differing results, from no association [19–21] to an increased risk [22].

Why consumption of alcohol was associated with a decline in visual acuity in Type 2 diabetes was unclear. Alcohol is known for its neurotoxic properties, which could induce oxidative damage to the retina and the optic nerve, leading to visual loss [4]. We observed that the size of association for deteriorating vision appeared to be stronger for beer and spirits than for wine. The natural antioxidants in wine may partially offset the adverse effects of alcohol [23]. Alcohol provides energy with little nutritive value and dietary intake of essential micronutrients,

including B vitamins and vitamin A, decreases with the increasing amount of alcohol consumed [24]. In addition, chronic consumption of alcohol alters the metabolism of vitamin A, depletes levels of hepatic vitamin A and causes visual loss [25].

Alternatively, the association between alcohol consumption and decline of visual acuity could be because of confounding effects. We demonstrated that our results were independent of the presence of cataract or macular oedema. It is possible that individuals who consume alcohol have different lifestyle characteristics that increase the risk of visual loss. Adjustment of cigarette smoking did not alter the association observed. However, residual confounding of unmeasured behaviours could not be ruled out. We had no information on social class. If participants in lower social classes both drank more alcohol and were less able to afford glasses with prescription, this would overestimate the reported association between alcohol consumption and the decline of visual acuity as visual measurement was performed corrected by glasses or contact lens, or through a pinhole. Nevertheless, we observed similar results when adjusting for factors associated with social class, such as BMI [26], smoking and exercise [27].

A strength of this study relates to its robust ascertainment of retinopathy, using mydriatic seven-field stereoscopic photography of both eyes, thereby reducing misclassification of endpoints. Another strength is its prospective design. In addition, the multi-centred design of the study allows the investigation of the ethnic differences in the patterns of alcohol consumption. Our study has potential limitations. Because of a limited number of cases of retinopathy, we may not have enough statistical power to detect associations with small effect sizes. The power further diminished when we stratified the analyses by ethnicity. Consumption of alcohol was measured by self report. Participants were asked to report the average number of standard drinks they consumed per week. The interpretation of 'a standard drink' may vary between participants. Any random measurement errors would attenuate the associations observed. However, individuals with strong social desirability may under-report their alcohol intake [28] and such systematic difference in reporting would bias the results in either direction. At present, there is no valid biomarker to measure alcohol consumption objectively. This study included specific questions on the frequency, the amount and the type of alcohol consumed, which has been shown to improve validity of the exposure measurement [29]. We do not have information on the strength and serving size of alcohol by country. However, adjusting for ethnicity and study centre did not alter our results.

Measuring visual acuity requires cooperation and adequate cognitive function of an individual to participate. Heavy consumption of alcohol can impair cognitive function [30]. Therefore, differential misclassification of outcomes (visual acuity) could have been present, which could over- or underestimate the true association. Of the various charts available to measure visual acuity, the Snellen chart is the one most commonly used in clinical settings. Although the Snellen notation is universally understood, the non-linear and non-geometric relationships of the sizes of the letters between successive lines could make it difficult to assess change over time [31]. Any random measurement errors would have attenuated the association observed. Alternatively, the logarithm of the minimum angle of resolution (logMAR) chart, with equal linear steps between lines, facilitates the analysis of change in visual acuity more effectively [32]. With respect to the reproducibility of visual score, a comparison of the ETDRS logMAR chart, the compact reduced logMAR chart and the Snellen chart indicated that these charts yield comparable results with similar test–retest variability [33]. Given the large number of study centres in different countries involved, to ensure that measuring and scoring visual acuity were consistent across study centres, the simple scoring system and the reduced testing time made the use of the Snellen chart and its notation preferable in this study.

In conclusion, these analyses of the AdRem study show that alcohol consumption is associated with an increased risk of deterioration of visual acuity, but not with progression of retinopathy in a population with Type 2 diabetes. We support further studies to confirm these findings.

Competing interests

JC has received honoraria and research funds, SH has received honoraria, MW has received honoraria and consulting fees, MM has received travel grants and honoraria, and BN and AP have received travel grants, honoraria and research funds, all from Servier. Servier is a co-sponsor of the ADVANCE Trial.

References

1 Adamis AP. Is diabetic retinopathy an inflammatory disease? *Br J Ophthalmol* 2002; **86**: 363–365.
2 Albert MA, Glynn RJ, Ridker PM. Alcohol consumption and plasma concentration of C-reactive protein. *Circulation* 2003; **107**: 443–447.
3 Greenfield JR, Samaras K, Jenkins AB, Kelly PJ, Spector TD, Campbell LV. Moderate alcohol consumption, estrogen replacement therapy and physical activity are associated with increased insulin sensitivity: is abdominal adiposity the mediator? *Diabetes Care* 2003; **26**: 2734–2740.
4 Bondy SC. Ethanol toxicity and oxidative stress. *Toxicol Lett* 1992; **63**: 231–41.
5 Moss SE, Klein R, Klein BE. The association of alcohol consumption with the incidence and progression of diabetic retinopathy. *Ophthalmology* 1994; **101**: 1962–1968.
6 Beulens JW, Kruidhof JS, Grobbee DE, Chaturvedi N, Fuller JH, Soedamah-Muthu SS. Alcohol consumption and risk of microvascular complications in type 1 diabetes patients: the EURODIAB Prospective Complications Study. *Diabetologia* 2008; **51**: 1631–1638.
7 Giuffre G, Lodato G, Dardanoni G. Prevalence and risk factors of diabetic retinopathy in adult and elderly subjects: The Casteldaccia Eye Study. *Graefes Arch Clin Exp Ophthalmol* 2004; **272**: 535–540.

8 Young RJ, McCulloch DK, Prescott RJ, Clarke BF. Alcohol: another risk factor for diabetic retinopathy? *Br Med J (Clin Res Ed)* 1984; **288**: 1035–1037.

9 Xu L, You QS, Jonas JB. Prevalence of alcohol consumption and risk of ocular diseases in a general population: the Beijing Eye Study. *Ophthalmology* 2009; **116**: 1872–1879.

10 Beulens JW, Patel A, Vingerling JR, Cruickshank JK, Hughes AD, Stanton A *et al.* Effects of blood pressure lowering and intensive glucose control on the incidence and progression of retinopathy in patients with type 2 diabetes mellitus: a randomized controlled trial. *Diabetologia* 2009; **52**: 2027–2036.

11 ADVANCE Research Group. Study rationale and design of ADVANCE: action in diabetes and vascular disease – preterax and diamicron MR controlled evaluation. *Diabetologia* 2001; **44**: 1118–1120.

12 Stolk RP, Vingerling JR, Cruickshank JK, Hughes AD, Stanton A, Juming L *et al.* Rationale and design of the AdRem study: evaluating the effects of blood pressure lowering and intensive glucose control on vascular retinal disorders in patients with type 2 diabetes mellitus. *Contemp Clin Trials* 2007; **28**: 6–17.

13 Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE *et al.* Risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. *UKPDS 50. Diabetologia* 2001; **44**: 156–163.

14 Stolk RP, van Schooneveld MJ, Cruickshank JK, Hughes AD, Stanton A, Lu J *et al.* Retinal vascular lesions in patients of Caucasian and Asian origin with type 2 diabetes: baseline results from the ADVANCE Retinal Measurements (AdRem) Study. *Diabetes Care* 2008; **31**: 708–713.

15 Peters HB. Vision screening with a Snellen chart. *Am J Optom Arch Am Acad Optom* 1961; **38**: 487–505.

16 Chong EW, Kreis AJ, Wong TY, Simpson JA, Guymer RH. Alcohol consumption and the risk of age-related macular degeneration: a systematic review and meta-analysis. *Am J Ophthalmol* 2008; **145**: 707–715.

17 Owen CG, Fletcher AE, Donoghue M, Rudnicka AR. How big is the burden of visual loss caused by age-related macular degeneration in the United Kingdom? *Br J Ophthalmol* 2003; **87**: 312–317.

18 Bressler NM. Age-related macular degeneration is the leading cause of blindness. *J Am Med Assoc* 2004; **291**: 1900–1901.

19 Manson JE, Christen WG, Seddon JM, Glynn RJ, Henneken CH. A prospective study of alcohol consumption and risk of cataract. *Am J Prev Med* 1994; **10**: 156–161.

20 Chasan-Taber L, Willett WC, Seddon JM, Stampfer MJ, Rosner B, Colditz GA *et al.* A prospective study of alcohol consumption and cataract extraction among US women. *Ann Epidemiol* 2000; **10**: 347–353.

21 Klein BE, Klein R, Lee KE, Meuer SM. Socioeconomic and lifestyle factors and the 10-year incidence of age-related cataracts. *Am J Ophthalmol* 2003; **136**: 506–512.

22 Lindblad BE, Hakansson N, Philipson B, Wolk A. Alcohol consumption and risk of cataract extraction a prospective cohort study of women. *Opthalmology* 2007; **114**: 680–685.

23 Estruch R, Sacanella E, Mota F, Chiva-Blanch G, Antuneza E, Casals E *et al.* Moderate consumption of red wine, but not gin, decreases erythrocyte superoxide dismutase activity: a randomized cross-over trial. *Nutr Metab Cardiovasc Dis* 2009; Oct 9. DOI: 10.1016/j.numecd.2009.07.006 [Epub ahead of print]

24 Guilland JC, Costa de Caryalho MJ, Moreau D, Boggio V, Lhuissier M, Fuchs F. Interrelationships of alcohol intake with blood vitamin status in nonalcoholic subjects. *Nutr Res* 1994; **14**: 1317–1330.

25 Lieber CS. Alcohol: its metabolism and interaction with nutrients. *Ann Rev Nutr* 2000; **20**: 395–430.

26 Berry TR, Spence JC, Blanchard C, Cutumisu N, Edwards J, Nykiforuk C. Changes in BMI over 6 years: the role of demographic and neighbourhood characteristics. *Int J Obes (Lond)* 2010; **34**: 1275–1283.

27 Stringhini S, Sabia S, Shipley M, Brunner E, Nabi H, Klyimaki M *et al.* Association of socioeconomic position with health behaviours and mortality. *J Am Med Assoc* 2010; **303**: 1159–1166.

28 Davis CG, Thake J, Vilhena N. Social desirability biases in self-reported alcohol consumption and harms. *Addict Behav* 2010; **35**: 302–311.

29 Feunekes GI, van't Veer P, van Staveren WA, Kok FJ. Alcohol intake assessment: the sober facts. *Am J Epidemiol* 1999; **150**: 105–112.

30 Chick JD, Smith MA, Engleman HM, Kean DM, Mander AJ, Douglas RH *et al.* Magnetic resonance imaging of the brain in alcoholics: cerebral atrophy, lifetime alcohol consumption, and cognitive deficits. *Alcohol Clin Exp Res* 1989; **13**: 512–518.

31 McGraw P, Winn B, Whitaker D. Reliability of the Snellen chart. *Br Med J* 1995; **310**: 1481–1482.

32 Ferris FL 3rd, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. *Am J Ophthalmol* 1982; **94**: 91–96.

33 Lim LA, Frost NA, Powell RJ, Hewson P. Comparison of the ETDRS log MAR, 'compact reduced logMar' and Snellen charts in routine clinical practice. *Eye* 2009; **24**: 673–677.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Members of the AdRem study staff.

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